

NIOSH-Interactive RadioEpidemiological Program (ver. 4.0b)
Technical Documentation

*****DRAFT*****

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The public may comment on NIOSH-IREP at any time. Comments can be sent electronically by e-mail to ocas@cdc.gov. The preferred formats for electronic documents sent by e-mail are MS Word or WordPerfect. Comments can be mailed to:

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I. Background

Under the Energy Employees' Occupational Illness Compensation Program Act (EEOICPA), the National Institute for Occupational Safety and Health (NIOSH) is charged with the development of guidelines to determine whether a claimant's cancer meets the criterion for causation by workplace exposure to ionizing radiation (i.e., a 50% or greater probability of causation).

The basis for this determination, as specified in EEOICPA, is the set of radioepidemiological tables developed by a National Institutes of Health Ad Hoc working group in 1985 (NIH 1985) as they are updated periodically. These radioepidemiological tables serve as a reference tool providing probability of causation estimates for individuals with cancer who were exposed to ionizing radiation. Use of the tables requires information about the person's dose, gender, age of exposure, date of cancer diagnosis and other relevant factors. The tables are used by the Department of Veterans Affairs (DVA) to make compensation decisions for veterans with cancer who were exposed in the line of duty to radiation from atomic weapon detonations. The primary source of data for the 1985 tables is research on cancer-related deaths occurring among Japanese atomic bomb survivors from World War II.

The 1985 tables are presently being updated by the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC) to incorporate progress in research on the relationship between radiation and cancer risk (NCI 2000). The draft update has been reviewed by the National Research Council (NAS/NRC 2000). HHS has employed the updated version of the tables, with certain modifications important to claims under EEOICPA, as a basis for determining probability of causation for employees covered under EEOICPA.

A scientific change achieved by the NCI update is the use of risk models developed from data on the occurrence of cancers (cases of illness) rather than the occurrence of cancer deaths among Japanese atomic bomb survivors. The risk models are based on more current data as well. Many more cancers have been modeled in the revised report. The new risk models also take into account factors that modify the effect of radiation on cancer, related to the type of radiation dose, the amount of dose, and the timing of the dose.

A major technological change accompanying this update, which represents a scientific as well as practical improvement, is the development of a computer software program for calculating probability of causation (also referred to as the assigned share). This software program, named the Interactive RadioEpidemiological Program (IREP), allows the user to apply the NCI risk models directly to data on an individual employee. This makes it possible to calculate probability of causation using better quantitative methods than could be incorporated into printed tables. In particular, IREP allows the user to take into account uncertainty concerning the information being used to calculate probability of causation. There typically is uncertainty about the radiation dose levels to which a person has been exposed, as well as uncertainty in the science relating levels of dose received to levels of cancer risk observed in study populations.

Accounting for uncertainty is important because it can have a large effect on the probability of causation estimates. DVA, in their use of the 1985 radioepidemiological tables, uses the value found in the tables at the upper 99 percent credibility limit of the probability of causation estimate. Similarly, as required by EEOICPA, the U.S. Department of Labor (DOL) will use the upper 99 percent credibility limit to determine whether the cancers of employees are

at least as likely as not caused by their radiation doses. This will help minimize the possibility of denying compensation to claimants under EEOICPA for those employees with cancers likely to have been caused by radiation exposures.

The risk models developed by NCI and CDC for IREP provided the primary basis for developing guidelines for estimating probability of causation under EEOICPA. They directly address 33 cancers and most types of radiation exposure relevant to employees covered by EEOICPA. These models take into account the employee's cancer type, year of birth, year of cancer diagnosis, and exposure information such as years of exposure, as well as the dose received from gamma radiation, x rays, alpha radiation, beta radiation, and neutrons during each year. The risk model for lung cancer takes into account smoking history as well. None of the risk models explicitly accounts for exposure to other occupational, environmental, or dietary carcinogens. Models accounting for these factors have not been developed and may not be possible to develop based on existing research. Moreover, DOL could not consistently or efficiently obtain the data required to make use of such models.

As stated above, the latest draft of the National Cancer Institute's IREP software has formed the basis of the NIOSH-IREP software. The NCI's latest draft has been updated from the version reviewed by the National Research Council in several ways. The updated draft includes a model for lung cancer resulting from radon exposure, developed from an analysis of U.S. uranium miner cohorts (RECA Committee, 1996). Other changes include the use of a modified method of modeling cancer risk from the Japanese atomic bomb survivor study, the incorporation of an uncertainty distribution for the latency of solid cancers, and the development of statistical distributions for the relative biological effectiveness (RBE) and dose and dose-rate effectiveness

factor (DDREF) of different energies of photons, neutrons, and alpha particles (Kocher et al. 2001). These changes are detailed in the NCI IREP documentation being developed by the NCI. It must be noted, however, that the NCI IREP is not finalized at the time of this writing. Changes in the NCI IREP that are relevant to the evaluation of compensation claims under EEOICPA may be incorporated into NIOSH-IREP prior to its finalization.

II. NIOSH-IREP and its implementation under EEOICPA

A. Dosimetry Issues

NIOSH-IREP includes twelve types of radiation exposure. Radon is considered an exposure that may contribute to risk of lung cancer only, and the remaining eleven types of exposure, considered for any cancer type, are described in Table 1. These types of exposures are differentiated by the assumed radiation weighting factor (termed here the relative biological effectiveness or RBE) and in some cases, a factor accounting for reduced or enhanced effectiveness in producing cancers resulting from dose protraction (dose and dose rate effectiveness factor, or DDREF). The distributions assumed for these factors are described in Section II.D below. There are two classes of electron (beta particle) exposure within NIOSH-IREP, one class associated with exposure to tritium, and a second class for all other electrons. Three different photon energy classes exist within NIOSH-IREP: photons of energy greater than 200 keV (exemplified by high-energy gamma radiation that was the primary exposure of the Japanese atomic bomb survivors), photons of energy between 30 and 200 keV, which includes photofluorographic x rays used during the 1940s and 1950s at some Department of Energy (DOE) facilities (Cardarelli 2000), and photons of energy less than 30 keV, which includes

photons emitted by certain transuranic radionuclides. There are five classes of neutrons differentiated by energy type. The most commonly encountered type of neutron exposure within the DOE workforce is fission neutrons, composed primarily of neutrons with energy between 100 keV and 2 MeV. However, neutrons of higher and lower energy are included because these exposures are relevant for certain DOE workers. Finally, a single class of radiation exposure is included for non-radon alpha particles. The exposure units used in NIOSH-IREP are working level months (WLM) for radon, and cSv (rem) for all other radiation types.

For each type of exposure, the dose used in NIOSH-IREP will be based on the individual organ or tissue in which the primary cancer occurred, or, if unavailable, in the nearest relevant organ or tissue. For bone cancer, dose to the endosteal cells (the cells of the outer bone surface) will be calculated. For skin cancer, a more site-specific approach will be used. Because studies of medically-exposed persons have shown that radiation-induced skin cancers tend to occur within the field of radiation exposure (van Daal et al. 1983, Shore et al. 1984, Hildreth et al. 1985, Lichter et al. 2000), skin dose will be calculated only for the location where the cancer occurred, as reflected in the 9th Revision of the International Classification of Diseases (ICD-9) 4-digit nosology code (i.e., lip, eyelid, ear, other parts of face, scalp and neck, trunk, upper limb, lower limb). If the body location is unspecified, the maximum skin dose at any location will be calculated as input to NIOSH-IREP.

In the dose reconstruction process, gamma and x ray doses will be considered acute over the smallest period of time during which the exposure measurement occurred. This is because it is not possible to discern the time period over which the radiation exposure occurred, within the monitoring period. As a practical matter, this means that the exposure rate will be categorized as

acute for each badge reading, and each will be specified separately within a given year in NIOSH-IREP. For example, if a claimant's dosimetry badges were exchanged and read on a quarterly basis, each of the four badge results would be entered as a separate acute dose (or dose distribution) in NIOSH-IREP. In contrast, photon exposures resulting from the intake of an internal emitter will be assumed to be chronic, as the decay path of the alpha particle (which is a known physical quantity) produces a chronic exposure. Because of uncertainty about the dose rate of exposures, neutron doses will be assumed to be chronic over the badge reading period. This assumption will have the effect of increasing the probability of causation for neutron exposures, because of the use of a protraction enhancement factor (e.g., see Section II.D and Kocher et al. 2001).

B. Cancers added to NIOSH-IREP

Certain cancer models have been added to NIOSH-IREP. These include cancers of the skin, bone, male breast, connective tissue, eye, and endocrine glands other than thyroid. The NCI version of IREP includes the last five of these in a general "residual" cancer model, but they are explicitly separated in NIOSH-IREP. The scientific basis of these models and their implementation in NIOSH-IREP are described below. In summary, the cancer sites used to produce excess relative risk (ERR) per Sv estimates for each risk model, and the cancer groupings to which these models were applied, are given in Table 2.

1. Bone cancer:

Exposure to plutonium has been found in numerous animal studies to cause bone cancer (NAS 1988). Most U.S. worker studies are based on relatively low exposures and small numbers of workers exposed to plutonium, and have thus been inconclusive with

respect to bone cancer induction. However, a recent study of the Russian Mayak facility (Koshurnikova et al. 2000) found elevated rates of bone cancer among workers with positive plutonium body burdens, after adjusting for cumulative external dose ($RR = 7.9$; 95% confidence interval = 1.6-32). Unfortunately, this study cannot be used for quantitative assessment of risk, because of serious limitations in the plutonium dosimetry for these workers (Koshurnikova et al. 2000); however, it provides strong qualitative evidence for an association between plutonium exposure and bone cancer in humans.

For the purposes of NIOSH-IREP, the basis of the bone cancer model is the risk analysis conducted for plutonium exposures among Rocky Flats workers (Grogan et al. 2000, 2001). For bone cancer, the sources of these researchers' risk analysis were the Japanese atomic bomb survivors studies (modified by the uncertain relative biological effectiveness for alpha particles as compared to low-energy photons and by the dose-and-dose rate effectiveness factor), studies of humans exposed to other alpha-emitters, and studies of animals exposed to plutonium. A subjectively weighted combination of these risk estimates for plutonium exposure was then used in the Grogan analysis to produce estimates of lifetime risk per unit dose and per unit intake of plutonium.

The approach of Grogan and colleagues is quite difficult to incorporate into IREP, however, because of the need of IREP to incorporate risks from many types of radiation exposure, not just plutonium and other alpha-emitting radionuclides. The problem with using human and animal studies of alpha-exposed groups as a source of risk coefficients in IREP is that, in the former, the risk per unit dose is expressed as a function of the initial (rather than the committed dose), while in the latter, the risk per unit dose is

expressed on an incremental basis. In other words, in the studies upon which the risk models are based, the radionuclide is deposited in the target organ (e.g., the bone surfaces), and the dose to bone surfaces is delivered throughout the life of the individual. The expression of risk in these studies is based on the initial exposure to the bone surface, which is an underestimate of the total dose received by the organ. While this is not an inconsistent approach for evaluating the risks of plutonium or other transuranic radionuclides, it is incompatible with the approach used throughout IREP. The model implemented by Grogan and colleagues that is most compatible with the approach of IREP is the bone cancer model obtained from Japanese atomic bomb survivors, modified by relevant distributions of RBE and DDREF for different types of radiation. Use of this approach is also consistent with that adopted by NCI for other tissues in which transuranic radionuclides tend to accumulate (e.g., liver).

The study of cancer incidence among atomic bomb survivors (Thompson et al. 1994) does not quantify bone cancer risks; however, the Grogan model uses excess risk estimates from the latest mortality study (Pierce et al. 1996) for its cancer incidence model. The NCI-IREP model for residual cancers includes bone cancer, among a diverse set of unrelated cancer types including cancers of the connective tissue, eye, male breast cancer, certain endocrine glands, and unspecified cancers. This residual-site model was deemed to be inappropriate for bone cancer in NIOSH-IREP, because of the strong evidence for radiogenicity of bone cancers (related to plutonium and other alpha-emitting radionuclides), and the dissimilarity of the cancers comprising the residual-site model. The excess relative risk estimates from the atomic bomb mortality study (Pierce et al.

1996) were used, therefore, as the basis for the risk coefficients in NIOSH-IREP. The bone cancer excess relative risk (ERR) was assumed to be constant after the minimum latency was reached (5 years), and no adjustment was made for either gender or age at exposure, due to the lack of information about these factors as risk modifiers.

The bone cancer ERR per Sievert from Table AII of Pierce et al. (1996) is 0.86, with an upper 95% confidence interval estimate of 3.70. A lognormal distribution using the upper confidence limit of the profile likelihood distribution to estimate the geometric standard deviation (GSD) was found to simulate well the entire profile likelihood distribution (see “Non-melanoma skin cancer model” discussion below). For bone cancer, therefore, the ERR per Sv was assumed to follow a lognormal distribution, with the geometric mean equal to the maximum likelihood estimate of the bone cancer ERR (0.86), and a GSD of 2.10. The GSD was calculated as follows:

$$\text{GSD} = e^{[\ln(\text{UC}) - \ln(\text{E})]/1.96}$$

where UC is the upper 97.5th percentile of the ERR per Sv distribution (3.70), and

E is the maximum likelihood estimate of the ERR per Sv (0.86).

2. *Non-melanoma skin cancer:*

Several studies have provided evidence that non-melanoma skin cancers, particularly basal cell carcinomas, are related to exposure to ionizing radiation (Shore 2001); and some expert groups consider skin cancer risk in establishing low-level skin radiation exposure limits (ICRP 1991a). These include studies of radiologists, uranium miners, and patients exposed during treatment for medical conditions, as well as the

Japanese atomic bomb survivors (Sevcova et al. 1978, van Daal et al. 1983, Hildreth et al. 1985, Thompson et al. 1994, Ron et al. 1998). Many studies suggest that, of the two types comprising non-melanoma skin cancer, basal cell carcinoma is more radiosensitive than squamous cell carcinoma (van Daal et al. 1983, Ron et al. 1998, Shore 2001); however, others do not specify the relative radiosensitivity of these two skin cancer types (Hildreth et al. 1985), or found similar radiosensitivity of the two types (Lichter et al. 2000).

Within NIOSH-IREP, only skin cancer has an adjustment for race and/or ethnicity in determining the probability of causation. Unlike other cancers, the biological justification for this adjustment is very strong: skin cancer incidence rates vary by a factor of 20 or more for individuals of different racial or ethnic groups. Most cancers that show racial variation in incidence differ by a factor of two or less (Fig. 1); however, for melanoma, incidence rates are 18-20 times greater among non-Hispanic U.S. whites than among African-Americans. Skin cancer incidence rates for Asian-Americans and Native Americans are similar to African-Americans (Miller and Gaudette 1996), and rates for Hispanic whites are intermediate between those of African-Americans and whites (Scotto et al. 1996). For most cancers, the reasons for disparity in incidence by race are not known, but probably include factors such as differences in tobacco use, dietary factors, and access to health care. In contrast, the reasons for racial and ethnic differences in skin cancer incidence rates appear strongly related to the damage produced by exposure to ultraviolet radiation (UV) in susceptible individuals. Non-whites are thought to be at less risk of cancer from exposure to UV through the protective effect of melanin, which absorbs harmful UV radiation in the skin (Kaidbey et al. 1979, Altman et al. 1987,

Kollias et al. 1991). The net effect of incorporating the background incidence rate of skin cancer is to properly reflect the increased probability of causation for radiation-induced skin cancer for non-white claimants, compared to whites exposed to the same doses under the same conditions, if a sub-multiplicative relationship exists between radiation exposure and sensitivity to UV radiation exposure. Not incorporating the ethnic differences in background risk would have the effect of underestimating the probability of causation of radiation-induced skin cancers among non-whites.

The form of the interaction between ionizing and UV radiation exposure is unclear. On theoretical grounds, ionizing radiation might be expected to interact additively with background risk (caused primarily by exposure of susceptible skin to UV radiation; UNSCEAR 2000b, p. 200), if melanin is not similarly protective of its effects. However, some studies have suggested that melanin provides protection from radiation-induced skin cancer as well (Harley et al. 1983, Shore et al. 1984, Davis et al. 1989). Unfortunately, few studies have evaluated formally the interaction of ionizing radiation exposure with skin pigmentation. A meta-analysis of twelve epidemiologic studies of UV and ionizing radiation exposed individuals could not distinguish between an additive and multiplicative interaction, due to the lack of controls with ionizing radiation exposure alone (Shore et al. 1990, UNSCEAR 2000b). Without the capability to formally test for the form of interaction within a study, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) recommends careful comparison of the relative risks among different populations in comparable studies (UNSCEAR 2000c, p. 310). The ICRP evaluated existing studies, and, given the findings of several studies that excess

absolute risk from ionizing radiation exposure is greatest among white populations (and is still higher in areas of the skin usually exposed to greater UV radiation), suggested an interaction that is more than additive (Harley et al. 1983, Shore et al. 1984; ICRP 1991a, pp. 75-78). However, a recent analysis of non-melanoma skin cancer among the Japanese atomic bomb survivors found excess relative risks per unit dose nearly ten times higher for areas of the body unexposed to UV radiation (Ron et al. 1998), which suggests a submultiplicative interaction between ionizing and UV radiation exposures.

The uncertainty in the appropriate form of interaction between UV and ionizing radiation exposure is expected to be most critical in determining the role of race or ethnicity in modifying the excess relative risk estimates produced from the Japanese atomic bomb survivor study. Because of this large uncertainty, the method of risk transfer from the Japanese to the U.S. racial/ethnic groups, built into the NIOSH-IREP program, should incorporate the possibility of an additive or multiplicative interaction (or a mixture of these). Given the evidence supporting a submultiplicative interaction between UV and ionizing radiation exposure and the theoretical support for an additive interaction between ionizing and UV radiation exposure, the IREP program uses the same uncertainty distribution for risk transfer as was used for breast cancer (i.e., favoring somewhat an additive risk transfer model).

No current U.S. rates are available for non-melanoma skin cancer, as this is not a reportable cancer among U.S. registries. However, a survey of non-melanoma skin cancer rates was carried out by researchers at the National Cancer Institute in the early 1980s, reflecting rates across a wide area within the U.S. for 1977-1980 (Scotto et al.

1983). In Japan, non-melanoma skin cancers are reportable, and incidence rates are available both for 1990 (Parkin et al. 1977) and for 1978-1982 (Muir et al. 1987). Therefore, to more accurately reflect comparative rates in both countries, incidence rates for the late 1970s (age-adjusted to the 1970 U.S. standard population) were used from both countries to estimate the risk transfer coefficients for NIOSH-IREP. For the U.S. population of non-Hispanic whites, these data were obtained from Tables 5 (males) and 6 (females) of Scotto et al. (1983). For Hispanic whites and African-Americans (Hispanic and non-Hispanic), these data were obtained from Scotto et al. (1996). The age-adjusted background incidence rates used in NIOSH-IREP are shown here in Table 3. Incidence rates for Asian or Native Americans have not been estimated in the special surveys of non-melanoma skin cancer incidence (Scotto et al. 1983, 1996). Based on literature reporting low rates of non-melanoma skin cancer risk among these groups (Miller and Gaudette 1996), as well as the similarity in malignant melanoma incidence among Native Americans, Asian-Americans and African-Americans (Table 3), the non-melanoma skin cancer incidence for the former two ethnic groups is assumed to be the same as for African-Americans, for purposes of NIOSH-IREP. While the background incidence rates for most cancers are based on relatively current rates (i.e., circa 1990), the rates for non-melanoma skin cancer for both the Japanese and U.S. populations are based on data from the late 1970s. More recent studies show that incidence rates have likely increased since that time (Miller and Weinstock 1994). This is not likely to be an unacceptable source of error for calculation of probability of causation within the DOE workforce, since claims

are to be considered for any cancer occurring since the worker began employment at a facility (i.e., a time period extending from the 1940s through the present day).

The appropriate form of dose-response model for skin cancer is highly uncertain (ICRP 1991a, p. 52). Some researchers advocate the use of a threshold model, on the basis of observations about dose-response relationships for such deterministic endpoints as skin dermatitis, desquamation and erythema, and upon evidence for a nonlinear dose-response relationship observed in some animal studies (reviewed in ICRP 1991a, pp 52-55). However, no evidence of a dose threshold was observed in a meta-analysis of twelve UV and ionizing radiation-exposed groups (Shore et al. 1990, UNSCEAR 2000b). A recent study evaluated various forms of the dose-response relationship for the atomic bomb survivors, and concluded that the best-fitting model for non-melanoma skin cancer is proportional to the fourth power of dose (Little and Charles 1997). However, a more recent analysis found no significant model improvement (over linearity) using a linear-quadratic model (Ron et al. 1998). A linear dose-response relationship for non-melanoma skin cancer has been advocated by others as well (e.g., Scotto et al. 1996). The mechanisms in skin carcinogenesis that might lead to a threshold, not observed for most other organs in these studies, are unclear (ICRP 1991a, pp. 54-55).

As for many cancer sites, skin doses are poorly estimated in most studies of risks associated with ionizing radiation exposure, making quantitative dose-response analysis difficult. An exception is the Japanese atomic bomb survivors study. For this reason, and to maximize consistency with the other risk modeling approaches in IREP, the latest basal cell skin carcinoma ERR per Sv estimates, obtained from Ron et al. (1998), were

incorporated into NIOSH-IREP (Table 4). The risk coefficients vary by age at exposure but not by gender, and were assumed to be linear in dose. For NIOSH-IREP, the distributions of ERR for each age-at-exposure category were approximated as lognormal, using the expected value as the geometric mean, and the published upper end of the 90% confidence interval (i.e., the 95th percentile of the distribution) to calculate the geometric standard deviation (GSD), as follows:

$$\text{GSD} = e^{[\ln(\text{UC}) - \ln(E)]/1.642}$$

where UC is the upper 95th percentile of the lognormal distribution, and E is the maximum likelihood estimate of the ERR per Sv.

The percentiles of this lognormal distribution of ERR/Sv were then generated from the resulting geometric mean and geometric standard deviation. The lognormal approximation, calculated using the method above, provided a very good fit to the profile likelihood distribution used for other cancer models to generate a distribution of ERR/Sv, particularly in the upper region of the distribution of ERR/Sv.

Although the risk models were developed for basal cell carcinomas, the ERR/Sv coefficients are applied to all non-melanoma skin cancers. This is because no age-specific risk coefficients are provided in the atomic bomb survivor analysis for squamous cell carcinomas, and because the ICD-9 categories for skin cancer do not distinguish squamous from basal cell carcinomas. The generated ERR/Sv distribution for each age at exposure is also incorporated into NIOSH-IREP for malignant melanoma. No adjustment is made for time since exposure (except the latency adjustment used for all other cancers

between 0 and 5 years after exposure). This is supported by evidence from several studies which indicate that radiation-related skin cancer risks remain elevated for many years following exposure (van Daal et al. 1983; Ron et al. 1998).

3. Malignant melanoma

The association between malignant melanoma and radiation is highly uncertain. Few studies have been conducted with sufficient power to detect increases in the relative risk of melanoma. This problem is exacerbated by the fact that background incidence rates are very low for some populations in which radiation-related risks have been evaluated. For example, the point estimate of radiation excess relative risk among atomic bomb survivors is high, but with a wide confidence interval, due to the very small number of cases (Ron et al. 1998). No significant excess of malignant melanoma was observed among the primarily African and Asian cohort of children exposed to radiation for the treatment of tinea capitis (scalp ringworm) in Israel (Ron et al. 1991). However, a small study of Israeli children exposed to x rays during cardiac catheterization showed elevated incidence of malignant melanoma (Modan et al. 2000). The radiation-related relative risk point estimate for melanomas was very similar to that for non-melanoma skin cancer in an irradiated North American population; however, the melanoma estimate was based on sparse data (Hildreth et al. 1985).

Most studies of DOE workers have shown no association between malignant melanoma and radiation exposure. However, early studies of workers at the Lawrence Livermore National Laboratory showed elevated incidence of malignant melanoma compared to the adjacent community, although risk was not associated with recorded

doses to ionizing radiation (Austin et al. 1981). This finding has been attributed by some to potentially increased surveillance among this population, and to important related factors, such as skin pigmentation and sunlight exposure patterns, which were not considered in the initial study (Hiatt et al. 1986, Moore et al. 1997). Other recent studies have concluded that, while surveillance bias may have partially contributed to the observed excess in malignant melanoma, an association with employment exposures including ionizing radiation persists after adjusting for confounding factors (Hiatt et al. 1993, Schwartzbaum et al. 1994, Austin and Reynolds 1997). Among other nuclear worker cohorts, skin cancer mortality (predominantly malignant melanoma) was found to be associated with external ionizing radiation dose in the U.K. National Registry of Radiation Workers cohort (Carpenter et al. 1994).

Direct quantitative estimates of radiation risk for malignant melanoma are not generally available. The risk estimates available in the Japanese atomic bomb survivor data have very wide confidence intervals, as they are based on only ten cases; however, they are consistent with the rates for non-melanoma skin cancer (Ron et al. 1998). Therefore, the ERR per Sv estimates for non-melanoma skin cancer were used to evaluate probability of causation for malignant melanoma. The sources of background incidence rates used in NIOSH-IREP for malignant melanoma of the skin are the same as for other cancers: Japanese incidence data were obtained from Parkin et al. (1997), and U.S. rates (race- and ethnicity-specific) were obtained from the U.S. Surveillance Epidemiology and End Results (SEER) program.

4. Male breast cancer

Breast cancer is extremely rare among men: the age-adjusted incidence is 0.7 per 100,000 among white males, compared to 90.7 per 100,000 for white females in the U.S. (Parkin et al. 1997). As a result, this cancer is very difficult to study directly in men, and little is known about risk factors for male breast cancer, with the exception of Klinefelter syndrome, a known major risk factor (Hultborn et al. 1997). A few sporadic cases among men given medical radiation treatment have been reported (Greene et al. 1983, Olsson and Ranstam 1988). However, some research has suggested, based on both mathematical models and on epidemiologic studies, that male breast cancer may have similar hormonally-related cancer promotion risk factors (e.g., high body weight and exposure to estrogen) as for female breast cancer (Casagrande et al. 1988, Bernstein et al. 1989, Thomas et al. 1992, Hsing et al. 1998). These hormonally-related risk factors have been found to interact multiplicatively with radiation, in studies of female Japanese atomic bomb survivors (Land et al. 1994). Thus, the excess relative risk of radiation-induced male breast cancer (applied to the background rates of males) may be similar to that of female breast cancer.

For NIOSH-IREP, ERR per Sv coefficients from female breast cancer models were used for male breast cancer. These were modified by the background incidence rates for male breast cancer in the U.S. and Japan, using the same data and procedures as for other cancer sites (Parkin et al. 1997, NCI 2000).

5. Connective tissue cancer, eye cancer, other endocrine cancer, and other and ill-defined sites

There is very little specific information about the radiogenicity of the following cancer groups:

- (1) connective and other soft tissue cancers (ICD-9 171),
- (2) cancer of the eye (ICD-9 190),
- (3) cancer of the endocrine glands other than thyroid (ICD-9 194), or
- (4) cancers of other, ill-defined and unspecified sites (ICD-9 196 and 199).

The NCI-IREP program contains a set of ERR per Sv coefficients derived from analysis of these and a few other sites, namely bone cancer and male breast cancer. To implement probability of causation models for the four groups above, the residual-site ERR per Sv model was applied to the background cancer incidence rates (U.S. and Japan) for each of the four groupings defined above, using data from Parkin et al. (1997). Thus, there are four additional models within NIOSH-IREP, for each of the four groupings described above (Table 2, 5).

C. Cancers excluded from NIOSH-IREP

1. Chronic lymphocytic leukemia (ICD-9 204.1).

No dose-response model was developed for chronic lymphocytic leukemia (CLL) by either the NIH Working Group (NIH 1985) or the NCI/CDC working group to update these tables (NCI 2000). This is because no elevation of CLL incidence was observed among Japanese atomic bomb survivors (Preston et al 1994). Because CLL is very rare

among non-Western populations (implying, therefore, that the power to detect small excess relative risks is poor in the atomic bomb survivors study), it is necessary to evaluate the relationship observed between radiation and CLL in other populations. No association of radiation exposure with CLL was observed among 14,000 British ankylosing spondylitis patients treated with x rays (a total of 2 CLL deaths; Darby et al. 1987). No elevation of CLL risk has been observed among U.S., Canadian and European women exposed to radiation during treatment for uterine cancer (a total of 57 CLL deaths; Curtis et al. 1994), nor has a relationship been observed in a large study of over 124,000 nuclear workers in the U.K. (Muirhead et al. 1999). Finally, no relationship was observed between external radiation dose and CLL in the first combined international nuclear workers study (a total of 27 CLL deaths; Cardis et al 1995). Studies of people exposed to internal sources of radiation have also not shown increased risks of CLL. For example, no increased risk was found for CLL among patients in Denmark exposed to Thorotrast, a ²³²Th-containing contrast medium (Andersson et al. 1993, IARC 2001)

In addition to these individual studies, most expert committees have listed CLL as a cancer that appears non-radiogenic. The BEIR V Committee report (NAS/NRC 1990) excluded CLL from the group of leukemias for which risk models were produced, based on the lack of an association found among the studies reviewed. The UNSCEAR 2000 report states that CLL appears to be non-inducible by radiation exposure (UNSCEAR 2000c, p. 308). In summary, chronic lymphocytic leukemia is strongly associated with attained age. No evidence has been found in published studies that ionizing radiation is associated with increased risk of CLL.

D. DDREF and RBE

As indicated in Section I of this report, changes in the DDREF and RBE distributions adopted in the latest revision of the draft NCI program were used in NIOSH-IREP. These changes include substantial modifications of the uncertainty distributions for the RBE, described in detail in the accompanying document (Kocher et al. 2001).

For DDREF, the NCI IREP program has adopted the uncertainty distribution used by Grogan et al. (2000), p. 6-23, for low linear energy transfer (LET) radiation (for cancers other than leukemia, breast and thyroid). This distribution has been adopted within NIOSH-IREP as well. The uncertainty distribution is a modified triangular distribution (see Kocher et al. 2001) similar to that recommended in NCRP (1997), with the incorporation of a small probability of a DDREF less than one (i.e., it allows the possibility of an inverse dose-rate effect for low-LET radiation). The justification for this change is the latest analyses of the Japanese atomic bomb survivor data (Pierce and Preston 2000), upon which the majority of IREP models are based. This analysis strongly supports a linear over a sublinear (e.g., linear-quadratic) model, even within the lowest dose categories. This change, reflecting a preference for the use of epidemiological data to estimate low-dose effects, also reflects that of the BEIR V committee, which stated (NAS/NRC 1990, p. 55):

“The committee felt strongly that its risk assessments should be based on human data to the extent that they were available and that animal data should be used only to address questions for which human data were unavailable or inadequate”.

The uncertainty distribution used in both NCI's and NIOSH's IREP is consistent with the large body of laboratory studies that demonstrate a reduced effect with dose protraction for

most cancers (IARC 2000, pp 301-304; UNSCEAR 2000a, pp 116-119), together with the latest analysis of the Japanese atomic bomb survivors, which suggests no reduction (and possibly, an enhancement) of carcinogenic effects at low doses. This DDREF distribution is used for chronic exposures, and is invoked for acute exposures below 0.2 Sv, according to the probability distribution used in NCI's original IREP methodology (NCI 2000).

The RBE distributions used in IREP vary for each different type of radiation (Table 7). The assumptions underlying these distributions are detailed in Kocher et al. (2001). In summary, the approach used to estimate the RBE for each type of radiation was to review the relevant literature comparing the RBE for the specific exposure type as compared to high-dose, high-energy photon radiation (i.e., the same exposure type as experienced by the Japanese atomic bomb survivors). For neutrons, the RBE distribution was estimated first for fission neutrons (those of energy between 100 keV and 2 MeV). For neutrons of higher or lower energy, an RBE reduction factor was applied, assuming a triangular distribution centered on the ICRP-recommended reduction factor of 2 or 4 (ICRP 1991b).

The RBE was assumed to be unity for photons of energy greater than 200 keV, as this is the primary exposure in the Japanese atomic bomb survivors studies, upon which the majority of the risk estimates are based. Photons of lower energy have an increased RBE, based on reviews of the relevant radiobiological literature. The RBE distributions assumed for electrons are also based on values obtained from review of the relevant literature (Kocher et al. 2001; Table 7).

For alpha radiation, the estimated RBE for chronic alpha exposure compared to low-dose-rate, low-LET exposure was centered on 24, with a lower and upper bound of 3 and 45, respectively (Kocher et al. 2001, Table 7).

The neutron RBE includes an adjustment, through a so-called enhancement factor, for a possible inverse dose-rate relationship for chronic exposures (Kocher et al. 2001; Table 7). This factor doubles the effect of a given dose for a chronic relative to an acute exposure. Conversely, no adjustment is currently made within NIOSH-IREP for a possible inverse dose rate relationship for alpha radiation. This phenomenon has been observed for many in vitro and animal studies, but it is thought to apply to a rather narrow range of LET and total dose (Brenner et al. 1992, 1993). An inverse dose-rate effect has also been observed in studies of radon-exposed workers (Hornung and Meinhardt 1987, Xuan et al. 1993, Tomasek et al. 1994); however, it has not been observed at doses below approximately 50 working level months (Lubin et al. 1995), nor has it been adopted in expert panel assessments of low-dose radon risk (NAS/NRC 1999). It is not clear at which dose level an inverse dose-rate effect should be incorporated for alpha radiation. It is, however, unlikely that alpha radiation exposures in the DOE workforce are comparable to levels at which an inverse dose-rate effect was observed among the uranium millers and miners. A specific inverse dose-rate effect is not included for alpha radiation exposures because it is implicitly incorporated into the RBE distribution for alpha radiation (Kocher et al. 2001).

E. Definitions of smoking categories for lung cancer claims

The NCI IREP program includes an adjustment to the probability of causation estimate for primary lung cancer, based on an assumed submultiplicative relationship between smoking and lung cancer (NCI 2000, pp. 48-50). There are seven smoking categories included in the NCI model (Table 6). No adjustments were made to this model for NIOSH-IREP; however, the definitions of the cancer categories require clarification for use under EEOICPA. The first

clarification needed is that only cigarette smoking history is considered. This is a result of precedent established in the first NIH Radioepidemiological Tables (NIH 1985), based on the strong, unambiguous, and quantifiable relationship between cigarette smoking and lung cancer (Baron and Rohan 1996). In addition, all smoking categories are defined *as of the date of the primary cancer diagnosis*. Lastly, additional clarification is given for the definitions of “never smoker” and “former smoker”. For EEOICPA, a “never smoker” is defined as a person who has smoked fewer than 100 cigarettes throughout his or her lifetime (prior to cancer diagnosis). Most epidemiologic studies define the “never smoker” category as never, rare or highly infrequent smokers (e.g., Rogot and Murray 1980, McLaughlin et al. 1995). This quantitative classification is currently in use by the CDC in several national surveys of smoking behavior (Anonymous 1994). A “former smoker” is an individual who ceased smoking cigarettes at least five years before the date of primary lung cancer diagnosis. This definition is adopted from the original NIH radioepidemiological tables, and is based on the observation that lung cancer background risks are not reduced for the first five years following smoking cessation (Rogot and Murray 1980).

III. Cancer model selection

The model to be used in NIOSH-IREP for each primary cancer is given in Table 5. For some cancers (e.g., certain leukemias) more than one IREP model will be employed. In this case, the model producing the highest probability of causation at the upper 99% credibility limit will be used as a basis for the compensation decision.

IREP models do not specifically include cancers as defined in their early stages: carcinoma in situ (CIS). These lesions are becoming more frequently diagnosed, as the use of cancer screening tools, such as mammography, have increased in the general population. The risk factors and treatment for CIS are frequently similar to those for malignant neoplasms, and, while controversial, there is growing evidence that CIS represents the earliest detectable phase of malignancy (Correa 1996, Kerlikowske et al. 1997, Grippo and Sandgren 2000), and they have been included in some evaluations of radiation-related cancer risks (Ron et al. 1998). Therefore, within NIOSH-IREP, CIS will be treated as a malignant neoplasm of the specified site.

Cancers identified by their secondary sites (sites to which a malignant cancer has spread), when the primary site is unknown, raise another issue for the application of IREP. This situation will most commonly arise when death certificate information is the primary source of a cancer diagnosis. It is accepted in medicine that cancer-causing agents such as ionizing radiation produce primary cancers. This means, in a case in which the primary site of cancer is unknown, the primary site must be established by inference to estimate probability of causation.

An evaluation of the relationship between primary and secondary cancer sites using the National Center for Health Statistics (NCHS) Mortality Database for years 1995-1997 was used to infer the primary site when only site of metastasis is known. Because national cancer incidence databases (e.g., the National Cancer Institute's Surveillance, Epidemiology and End Results program) do not contain information about sites of metastasis, the NCHS database was considered the best available data source to assign the primary site(s) most likely to have caused the spread of cancer to a known secondary site. For each secondary cancer, the set of primary cancers producing approximately 75% of that secondary cancer among the U.S. population was

identified (males and females were considered separately; Table 8). Therefore, for secondary cancers with unknown primary site, this table will be used to select likely primary sites, which will each then be evaluated using NIOSH-IREP.

If no primary or secondary cancer site is specified (i.e., the cancer is identified as ICD-9 199, with no secondary cancer site specified), then the model for “Other and ill-defined sites” should be used (Table 2, 5).

IV. Limitations of NIOSH-IREP

As stated previously, the basis of NIOSH-IREP is the set of methods and models developed by the National Cancer Institute, which updated the 1985 Radioepidemiological Tables developed by a National Institutes of Health working group. The National Research Council (NAS/NRC 2000) identified some limitations to the methods used in the first draft of NCI-IREP, many of which were addressed by NCI in the version that is the basis of NIOSH-IREP. The NCI report (NCI 2000) considers the current IREP software to be an interim product that may require substantial revision after the publication of the consensus of the BEIR VII committee.

Several limitations existing in the revised NCI methods could not be addressed in NIOSH-IREP, due to the very short time frame established by the regulation. The following list describes some of these limitations. It is anticipated that these and other limitations will be remedied in future versions of NIOSH-IREP.

- A. For EEOICPA, the ideal source population from which to develop risk estimates for probability of causation calculation is the DOE workforce itself, particularly for

- exposures to alpha radiation. Despite the finding of excess cancers among some DOE populations, at present it is difficult to use these findings in a quantitative risk assessment, because of uncertainties about confounding exposures (like chemical exposures), complex patterns and timings of exposure and disparate findings among different populations. It is likely that future research will provide a better basis for quantitative risk assessment using data that relates directly to the DOE workforce.
- B. Large changes in cancer incidence over time exist for many cancers (e.g., breast, lung, prostate); however, the background rates have been fixed at a single point in time (usually, 1990). Failing to incorporate these changes could lead to an overestimation or underestimation of a claimant's probability of causation.
- C. Some of the source models for risk coefficients have unquantified uncertainty related to the latency between exposure and cancer incidence. For example, the excess relative risk of leukemia between 2 and 5 years following exposure is unknown, because the follow-up time for the Japanese atomic bomb survivors began 5 years after the exposure. Excess relative risks between 2 and 5 years after exposure may be different than those 5 or more years after exposure. This limitation is less likely to exist for other cancer types because of the generally longer latency for most cancers.
- D. The assumed form of interaction between UV radiation exposure or susceptibility (as reflected by racial and ethnic differences in background skin cancer risk) and radiation exposure is highly uncertain, and has not been evaluated formally through a thorough assessment (or meta-analysis) of the relevant literature. Similarly, formal

- evaluations of the risk factor interactions for many cancers (e.g., breast and stomach) could further elucidate the appropriate form of risk transfer between the Japanese and U.S. populations. Additionally, a non-melanoma skin cancer model that incorporates age-adjustment for both squamous and basal cell carcinoma would be an improvement over the current model.
- E. The dose and dose-rate effectiveness factor (DDREF) uncertainty distribution for low-dose, low dose-rate exposure used in NCI's and NIOSH's IREP currently has a large influence on the calculated probability of causation values. This factor merits further attention with respect to the potential application of an inverse dose-rate effect for alpha radiation exposure, and to the appropriate weighting to use for various values (including less than one) of the RBE, for low-dose, chronic photon exposures.

Figure 1. U.S. White and African-American cancer excess incidence ratio (calculated as higher rate divided by lower rate, minus 1), for cancers showing heterogeneity by race (data from Parkin et al. 1997). Bars extending to the left indicate cancers that have higher incidence rates among African-Americans, and bars extending to the right indicate cancers with higher incidence rates among whites.

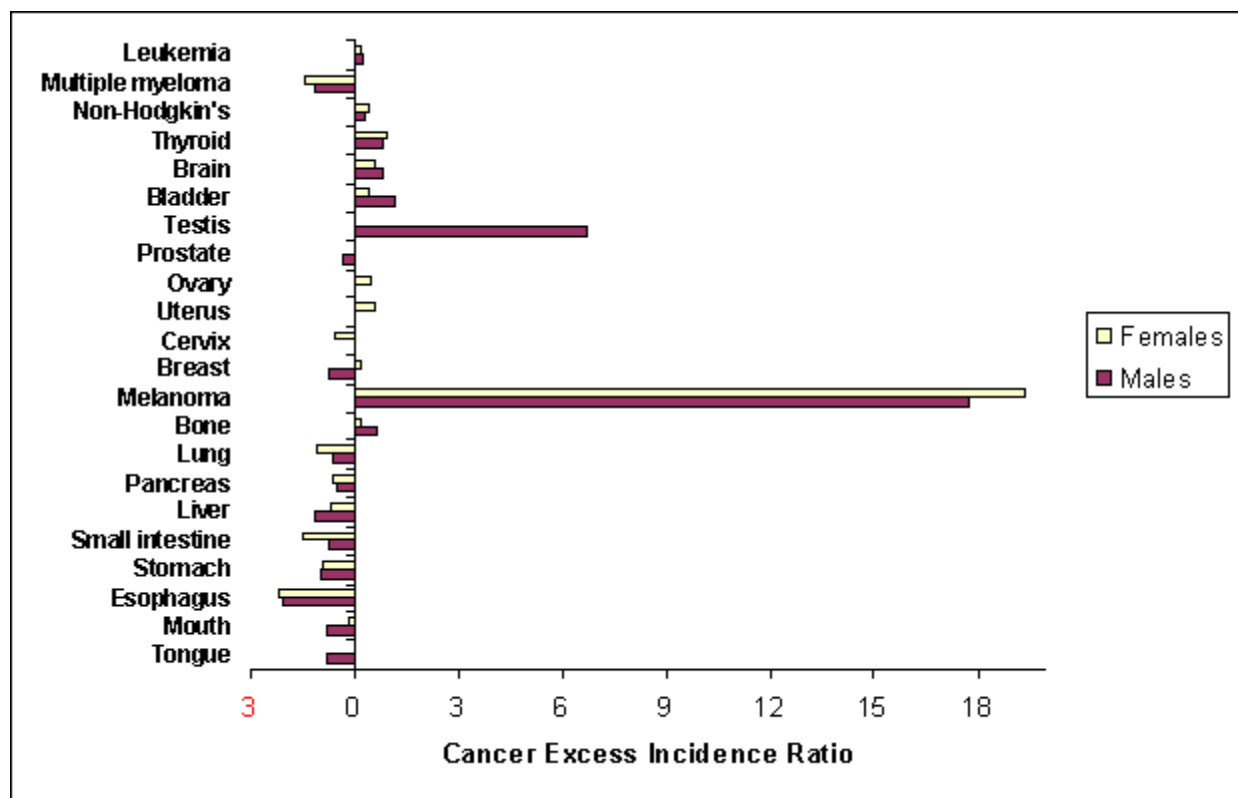


Table 1. Radiation exposure types in NIOSH-IREP.

Exposure type	Energy range	Typical exposure scenario
Radon (lung cancer only)	All	Exposure occurs near large sources of radium-bearing material such as the K-65 material at Fernald, or storage of radium in drums.
Electron (source other than tritium)	> 14 keV	Exposure typically results from processing and/or handling of fission products, such as Sr-90, or activation products, such as Co-60. Exposure can also result from uranium handling or processing operations.
Electron (tritium)	$E_{\beta\text{max}} = 14 \text{ keV}$	Exposure typically occurs around tritium production facilities such as Savannah River and Mound, but can also result from nuclear reactor operations or nuclear weapons assembly or research.
Photon	<30 keV	Low-energy x rays from transuranic isotopes such as plutonium.
Photon	30-200 keV	Medium-energy photons are typically encountered from scatter of higher energy photons. These photons can also result from gamma emissions of certain transuranic isotopes such as americium, and are the primary energy found in early stereoscopic x rays.
Photon	>200 keV	High-energy photons are the most common of the three categories listed. These are typically encountered from work with the nuclear fuel cycle from fuel manufacturing, reactor operations, spent nuclear fuel processing, decontamination and decommissioning activities and waste monitoring and storage.
Neutron	<10 keV	Low-energy neutrons exposures include thermal neutrons commonly found around nuclear reactors.
Neutron	10-100 keV	Intermediate-energy neutron exposure can occur around nuclear reactors as neutrons are moderated from high energy to thermal energies.
Neutron (fission)	100 keV-2 MeV	Neutron exposure typically encountered during the operation of a nuclear reactor. This energy of neutron exposure can also be encountered from work with californium neutron sources
Neutron	2-20 MeV	Reactions between alpha particles from materials such as plutonium or polonium and light materials such as beryllium resulting the production of neutrons. These reactions are commonly called (α ,n) reactions. This range also includes 14 MeV neutrons from fusion reactions.
Neutron	>20 MeV	Exposure to neutrons greater than 20 MeV can result from work around accelerators.
Alpha	All	Primary exposure hazard is internal radiation following the inhalation or ingestion of an alpha emitting radionuclides such as plutonium, uranium, americium, polonium, actinium, and thorium.

Table 2. Cancer sites as source for excess relative risk (ERR) per Sv coefficients for risk models in NIOSH-IREP, and cancer group to which model should be applied.

Cancer models in NIOSH-IREP	Cancer site used as source of ERR/Sv (ICD-9 code)	ICD-9 codes of background rates
Oral Cavity and Pharynx (140-149)	140-149	140-149
Esophagus (150)	150	150
Stomach (151)	151	151
Colon (153)	153	153
Rectum (154)	154	154
All digestive (150-159)	150-159	150-159
Liver (155.0)	155.0	155.0
Gallbladder (155.1, 156)	155.1,156	155.1,156
Pancreas (157)	157	157
Trachea, Bronchus and Lung (162)	162	162
Other respiratory (nasal cavity, larynx and other, 160, 161, 163-165)	160, 161, 163-165	160, 161, 163-165
Bone (170)	170	170
Connective tissue (171)	170, 171, 175, 190, 194, 195	171
Malignant melanoma (172)	173	172
Non-melanoma skin (173)	173	173
Breast-female (174)	174	174
Breast-male (175)	174	175
Ovary (183)	183	183
Female genitalia less ovary (179-182, 184)	179-182, 184	179-182, 184
All male genitalia (185-187)	185-187	185-187

Cancer models in NIOSH-IREP	Cancer site used as source of ERR/Sv (ICD-9 code)	ICD-9 codes of background rates
Bladder (188)	188	188
Kidney and other urinary organs (188-189)	188-189	189
Eye (190)	170, 171, 175, 190, 194, 195	190
Nervous system (191, 192)	191, 192	191, 192
Thyroid (193)	193	193
Other endocrine glands (194)	170, 171, 175, 190, 194, 195	194
Other and ill-defined sites (195, 199)	170, 171, 175, 190, 194, 195	195
Lymphoma and Multiple Myeloma (200-203)	200-203	200-203
Leukemia, less chronic lymphocytic leukemia (204-208, less 204.1)	204-208, less 204.1	204-208, less 204.1
Acute lymphocytic leukemia (204.0)	204.0	204.0
Acute myelogenous leukemia (205.0)	205.0	205.0
Chronic myelogenous leukemia (205.1)	205.1	205.1

Table 3. U.S. skin cancer incidence rates used in NIOSH-IREP. 1990 Malignant melanoma incidence rates for Japan are adapted from Parkin et al. (1997) and for the U.S. are from SEER program (April 1999 public use datafile). 1978-1982 non-melanoma skin cancer incidence rates for Japan are from Parkin et al. (1997), and for three U.S. ethnic groups are from Scotto et al. (1983, 1996).

	Age-adjusted incidence rate, per 100,000 persons annually (standard error)					
	Japanese ¹	U.S. Native American	U.S. Asian and Pacific Islander	U.S. African-American	U.S. White Hispanic	U.S. White Non-Hispanic
Malignant melanoma ² , 1990 rates						
Males	0.48 (0.09)	0.66 (0.30)	1.01 (0.11)	0.82 (0.10)	2.29 (0.15)	16.4 (0.15)
Females	0.43 (0.08)	1.26 (0.33)	0.77 (0.09)	0.55 (0.07)	2.44 (0.14)	11.9 (0.13)
Non-melanoma skin cancer ³ , 1978-1982 rates						
Males	6.05 (0.65)	N/A ⁴	N/A	4.1 (1.3)	61.6 (4.8)	312 (2.4)
Females	4.42 (0.48)	N/A	N/A	4.5 (0.76)	45.1 (3.5)	173 (1.6)

¹Japanese rates are weighted rates from Hiroshima (2/3) + Nagasaki (1/3) Prefectures

²Rates are age-adjusted to 1940 World standard population

³Rates are age-adjusted to 1970 U.S. standard population

⁴N/A: not available

Table 4. Risk coefficients used for skin cancer model (obtained from Ron et al. 1998).

Age at exposure (years)	Excess relative risk per Sievert	
	Geometric mean	Geometric standard deviation
Skin cancer		
0-9	21	2.14
10-19	6.7	1.76
20-39	1.7	1.63
≥ 40	0.70	2.01

Table 5. Cancer models to be used in calculation of probability of causation. Abbreviations: MN (malignant neoplasm), CIS (carcinoma in situ), NUB (neoplasm of uncertain behavior), NUN (neoplasm of unspecified nature).

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
Malignant neoplasm (MN) of lip, oral cavity and pharynx	140-149	Oral cavity and pharynx
MN of esophagus	150	Esophagus
MN of stomach	151	Stomach
MN of small intestine	152	All digestive
MN of colon	153	Colon
MN of rectum and anus	154	Rectum
MN of liver	155.0, 155.2	Liver
MN of gall bladder and bile ducts	155.1, 156	Gall bladder
MN of pancreas	157	Pancreas
MN of retroperitoneum and peritoneum	158	All digestive
MN of other digestive	159	All digestive
MN of nasal cavities, middle ear, and sinuses	160	Other respiratory
MN of larynx	161	Other respiratory
MN of trachea, bronchus and lung	162	Lung
MN of pleura	163	Other respiratory
MN of thymus, heart and mediastinum	164	Other respiratory
MN of other respiratory organs	165	Other respiratory
MN of bone	170	Bone

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
MN of connective tissue	171	Connective tissue
Malignant melanoma	172	Malignant melanoma
MN of other skin	173	Non-melanoma skin
MN of breast	174, 175	Breast
MN of uterus or uterine cervix	179, 180, 182	Female genitalia less ovary
MN of ovary	183	Ovary
MN of other female genital	181, 184	Female genitalia less ovary
MN of male genital	185-187	All male genitalia
MN of urinary bladder	188	Bladder
MN of kidney and other urinary organs	189	Urinary organs less bladder
MN of eye	190	Eye
MN of brain and other nervous system	191, 192	Nervous system
MN of thyroid gland	193	Thyroid
MN of other endocrine glands	194	Other endocrine glands
MN of other and ill-defined sites	195	Other and ill-defined sites
Non-Hodgkin's lymphoma and other lymphoid tissue, Hodgkin's disease	200-202	Lymphoma and multiple myeloma
Multiple myeloma and other immunoproliferative diseases	203	Lymphoma and multiple myeloma
Acute and unspecified lymphocytic leukemia	204.0, 204.9	Acute lymphoid leukemia
Subacute and other (not chronic) lymphoid leukemia	204.2, 204.8	Leukemia, less CLL

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
Acute and unspecified myelogenous leukemia	205.0, 205.9	Leukemia, less CLL AND Acute myeloid leukemia
Chronic myelogenous leukemia	205.1	Leukemia, less CLL AND Chronic myeloid leukemia
Subacute myelogenous leukemia, myeloid sarcoma, and other myeloid leukemia	205.2, 205.3, 205.8	Leukemia, less CLL
Monocytic leukemia, other specified leukemia	206, 207	Leukemia, less CLL
Acute leukemia of unspecified cell type	208.0	Leukemia, less CLL AND Acute lymphoid leukemia, AND Acute myeloid leukemia
Chronic leukemia of unspecified cell type	208.1	Leukemia, less CLL AND Chronic myeloid leukemia
Carcinoma in situ (CIS) of lip, oral cavity and pharynx	230.0	Oral cavity and pharynx
CIS of esophagus	230.1	Esophagus
CIS of stomach	230.2	Stomach
CIS of colon	230.3	Colon
CIS of rectum, anal canal, and anus	230.4, 230.5, 230.6	Rectum
CIS of liver and biliary system	230.8	Liver
CIS of other and unspecified intestine, digestive organs	230.7, 230.9	All digestive
CIS of larynx and other respiratory	231.0, 231.8, 231.9	Other respiratory
CIS of lung	231.1, 231.2	Lung
CIS of skin	232	Malignant melanoma AND Non-melanoma skin
CIS of breast	233.0	Breast

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
CIS of cervix uteri or other and unspecified parts of uterus	233.1, 233.2	Female genitalia, less ovary
CIS of other and unspecified female genital organs	233.3	Female genitalia, less ovary AND Ovary
CIS of prostate, penis or other and unspecified male genital organs	233.4	All male genitalia
CIS of bladder	233.7	Bladder
CIS of other and unspecified urinary organs	233.9	Urinary organs less bladder
CIS of eye	234.0	Eye
CIS of other and unspecified sites	234.8, 234.9	Other and ill-defined sites
Neoplasm of uncertain behavior (NUB) of salivary gland, lip, oral cavity or pharynx	235.0, 235.1	Oral cavity and pharynx
NUB of stomach	235.2	Stomach
NUB of colon	235.2	Colon
NUB of rectum and anus	235.2	Rectum
NUB of liver and biliary passages	235.3	Liver
NUB of retroperitoneum and peritoneum, and other and unspecified digestive organs	235.4, 235.5	All digestive
NUB of larynx, pleura, thymus, mediastinum, and other and unspecified respiratory organs	235.6, 235.8, 235.9	Other respiratory
NUB of trachea, bronchus and lung	235.7	Lung

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
NUB of uterus, and other and unspecified female genital organs	236.0, 236.1, 236.3	Female genitalia, less ovary
NUB of ovary	236.2	Ovary
NUB of prostate, testis and other male genital	236.4, 236.5, 236.6	All male genitalia
NUB of bladder	236.7	Bladder
NUB of other and unspecified urinary tract, and suprarenal gland	236.9, 237.2	Urinary organs less bladder
NUB of pituitary, pineal and other and unspecified endocrine glands	237.0, 237.1, 237.4	Thyroid
NUB of paraganglia, brain and spinal cord, and other nervous system	237.3, 237.5, 237.6, 237.7, 237.9	Nervous system
NUB of bone and articular cartilage	238.0	Bone
NUB of connective and other soft tissue	238.1	Connective tissue
NUB of skin	238.2	Malignant melanoma AND Non-melanoma skin
NUB of breast	238.3	Breast
NUB of other lymphatic and hematopoietic	238.5-238.7	Lymphoma and multiple myeloma
NUB of other specified and unspecified sites	238.8, 238.9	Other and ill-defined sites
Neoplasm of unspecified nature (NUN) of digestive system	239.0	All digestive
NUN of respiratory system	239.1	Lung AND Other respiratory
NUN of bone and soft tissue	239.2	Bone

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
NUN of skin	239.2	Non-melanoma skin
NUN of breast	239.3	Breast
NUN of bladder	239.4	Bladder
NUN of other genitourinary organs	239.5	Female genital less ovary AND Ovary AND All urinary organs (if female) All male genital AND All urinary organs (if male)
NUN of brain and other parts of nervous system	239.6, 239.7	Nervous system
NUN of endocrine glands	239.7	Thyroid AND Other endocrine glands
NUN of other specified or unspecified sites	239.8, 239.9	Other and ill-defined sites

Table 6. Smoking category definitions for lung cancer claims under NIOSH-IREP

Smoking category	Definition
Never	Smoked fewer than 100 cigarettes (throughout lifetime) prior to cancer diagnosis
Former	Quit smoking five years or more before date of cancer diagnosis
Current (? cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), quantity unknown
Current (<10 cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), average of fewer than 10 cigarettes per day
Current (10-19 cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), average of 10-19 cigarettes per day
Current (20-39 cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), average of 20-39 cigarettes per day
Current (40+ cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), average of 40 or more cigarettes per day

Table 7. Summary of relative biological effectiveness (RBE) factors to be used in estimating probability of causation of cancers from exposure to various radiation types. For description of radiation weighting factors (w) and other terms, see Legend on page following table.

RBE factors to be used with risk coefficients derived from exposures at high doses and high dose rates of gamma radiation and adjusted to low doses and dose rates by use of DDREF _{γ}					
Exposure information		Estimated RBE factor			
Radiation type	Exposure rate	Description	95% confidence interval		
			2.5 th	50 th	97.5 th
Electrons	Any ^a				
All except tritium		Single-valued	—	1.0	—
Tritium		Triangular (1, 2, 5)	1.3	2.6	4.4
Photons	Any ^a				
E>200 keV		Single-valued	—	1.0	—
E=30-200 keV		$w_{R,L}(X)$	1.9	2.7	3.7
E<30 keV		$w_{R,L}(X) \times \text{Triangular (1, 1.3, 1.6)}$	2.4	3.4	5.0
Neutrons		Not applicable			
Alpha particles	Chronic ^b	$w_{R,L}(\alpha)$	7.7	24	40

RBE factors to be used with risk coefficients derived from exposure to high doses and high dose rates of gamma radiation

Electrons Not applicable

Photons Not applicable

Neutrons^c

E=0.1-2 MeV ^d	Acute	$w_{R,H}(n)$	1.2	4.9	20
	Chronic	$w_{R,H}(n) \times EF$	1.3	6.4	30
E=10-100 keV or E=2-20 MeV	Acute	$w_{R,H}(n)/AF_2$	1.0	2.3	9.4
	Chronic	$w_{R,H}(n) \times EF/AF_2$	1.0	3.0	13
E<10 keV or E>20 MeV	Acute	$w_{R,H}(n)/AF_4$	1.0	1.1	4.6
	Chronic	$w_{R,H}(n) \times EF/AF_4$	1.0	1.5	7.2

Alpha particles Not applicable

Footnotes for Table 7

^aFor acute exposures to photons or electrons, risk coefficients are adjusted by a $DDREF_\gamma$ that depends on the dose received. For acute doses greater than 20 cSv, $DDREF_\gamma = 1.0$. For acute doses less than 20 cSv, a $DDREF_\gamma$ different from unity is applied, and its value approaches $DDREF_\gamma$ for chronic exposures as the dose approaches zero.

^bExposures to alpha particles emitted by radionuclides generally should be chronic.

^cThe lower tail of the aggregate probability distribution for each exposure situation is truncated at 1.0, based on an assumption that the biological effectiveness of neutrons should not be greater than that of high-energy photons.

^dThe RBE factors for this energy range apply to fission neutrons.

See following page for Legend for Table 7.

Legend for Table 7

RBE factor	Relative biological effectiveness factor obtained by combining radiation weighting factor for a given radiation type with any applicable modifying factors.
$w_{R,L}(X)$	Radiation weighting factor for X rays and gamma rays of energy <200 keV. Probability distribution assumed to be lognormal (GM=2.65; GSD=1.19).
$w_{R,H}(n)$	Radiation weighting factor for fission neutrons derived from experiments using high acute doses of high-energy gamma radiation. Probability distribution assumed to be lognormal (GM=4.89; GSD=2.05).
EF	Enhancement factor to account for inverse dose-rate effect; applies only to chronic exposures to neutrons of any energy. Probability distribution assumed to be discrete (50% at 1.0, 25% at 1.5, 25% at 2).
AF ₂	Energy-dependent reduction in biological effectiveness, relative to fission neutrons, for neutrons of energy 10-100 keV or 2-20 MeV. Probability distribution assumed to be triangular (min=1.5, mode=2, max=3).
AF ₄	Energy-dependent reduction in biological effectiveness, relative to fission neutrons, for neutrons of energy <10 keV or >20 MeV. Probability distribution assumed to be triangular (min=3, mode=4, max=6).
$w_{R,L}(\alpha)$	Radiation weighting factor for alpha particles derived from experiments using low dose rates of low-LET reference radiations. Probability distribution assumed to be triangular (min=3, mode=24, max=45).
DDREF _{γ}	Dose and Dose-Rate Effectiveness Factor used to adjust risk coefficients derived from exposures at high doses and high dose rates of high-energy gamma radiation in cases of exposure at low doses and dose rates of low-LET radiations.

Table 8. Primary cancers (ICD-9 codes⁵) for which probability of causation is to be calculated, if only a secondary cancer site is known. “M” indicates cancer site should be used for males only, and “F” indicates cancer site should be used for females only.

Secondary cancer	ICD-9 code of likely primary cancers
Lymph nodes of head, face and neck (196.0)	141, 142 (M), 146 (M), 149 (F), 161 (M), 162, 172, 173, 174 (F), 193 (F)
Intrathoracic lymph nodes (196.1)	150 (M), 162, 174 (F)
Intra-abdominal lymph nodes (196.2)	150 (M), 151 (M), 153, 157 (F), 162, 174 (F), 180 (F), 185 (M), 189, 202 (F)
Lymph nodes of axilla and upper limb (196.3)	162, 172, 174 (F)
Inguinal and lower limb lymph nodes (196.5)	154 (M), 162, 172, 173 (F), 187 (M)
Intrapelvic lymph nodes (196.6)	153 (M), 154 (F), 162 (M), 180 (F), 182 (F), 185 (M), 188
Lymph nodes of multiple sites (196.8)	150 (M), 151 (M), 153 (M), 162, 174 (F)
Lymph nodes, site unspecified (196.9)	150 (M), 151, 153, 162, 172, 174 (F), 185 (M)
Lung (197.0)	153, 162, 172 (M), 174 (F), 185 (M), 188 (M), 189
Mediastinum (197.1)	150 (M), 162, 174 (F)
Pleura (197.2)	150 (M), 153 (M), 162, 174 (F), 183 (F), 185 (M), 189 (M)
Other respiratory organs (197.3)	150, 153 (M), 161, 162, 173 (M), 174 (F), 185 (M), 193 (F)
Small intestine, including duodenum (197.4)	152, 153, 157, 162, 171, 172 (M), 174 (F), 183 (F), 189 (M)

⁵The International Classification of Diseases Clinical Modification (9th Revision) Volume I&II. [1991] Department of Health and Human Services Publication No. (PHS) 91-1260, U.S. Government Printing Office, Washington D.C.

Secondary cancer	ICD-9 code of likely primary cancers
Large intestine and rectum (197.5)	153, 154, 162, 174 (F), 183 (F), 185 (M)
Retroperitoneum and peritoneum (197.6)	151, 153, 154 (M), 157, 162 (M), 171, 174 (F), 182 (F), 183 (F)
Liver, specified as secondary (197.7)	151 (M), 153, 154 (M), 157, 162, 174 (F)
Other digestive organs (197.8)	150 (M), 151, 153, 157, 162, 174 (F), 185 (M)
Kidney (198.0)	153, 162, 174 (F), 180 (F), 185 (M), 188, 189, 202 (F)
Other urinary organs (198.1)	153, 174 (F), 180 (F), 183 (F), 185 (M), 188, 189 (F)
Skin (198.2)	153, 162, 171 (M), 172, 173 (M), 174 (F), 189 (M)
Brain and spinal cord (198.3)	162, 172 (M), 174 (F)
Other parts of nervous system (198.4)	162, 172 (M), 174 (F), 185 (M), 202
Bone and bone marrow (198.5)	162, 174 (F), 185 (M)
Ovary (198.6)	153 (F), 174 (F), 183 (F)
Suprarenal gland (198.7)	153 (F), 162, 174 (F)
Other specified sites (198.8)	153, 162, 172 (M), 174 (F), 183 (F), 185 (M), 188 (M)

V. References

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Appendix I: NIOSH-IREP program output

NIOSH-Interactive RadioEpidemiological Program

Probability of Causation Results

Date of run: October 9, 2001

DOL Claim Center: Denver, CO

Time of run: 2:02 p.m.

NIOSH-IREP version: 4.0b

Claim #: 000001-DE

Claimant SSN: 000-00-0000

Claimant name: John Q. Doe

CLAIMANT CANCER DIAGNOSES:

Primary cancer #1: Prostate (ICD-9 185)

Date of diagnosis: 10/20/1988

Primary cancer #2: N/A

Date of diagnosis: N/A

Primary cancer #3: N/A

Date of diagnosis: N/A

Secondary cancer #1: Lung (ICD-9 197.0)

Date of diagnosis: 03/13/1994

Secondary cancer #2: N/A

Date of diagnosis: N/A

Secondary cancer #3: N/A

Date of diagnosis: N/A

CLAIMANT INFORMATION USED IN PROBABILITY OF CAUSATION CALCULATION:

Gender: M

Race (skin cancer only): N/A

Birth Year: 1920

Year of Diagnosis: 1988

Cancer model: All male genitalia

Should alternate cancer model be run? No

Smoking history (trachea, bronchus or lung cancer only): N/A

NIOSH-IREP ASSUMPTIONS AND SETTINGS:

User-Defined Uncertainty Distribution: Lognormal(1,1)

Number of Iterations: 2000

Random number seed: 99

EXPOSURE INFORMATION:

Exposure File Name: XXXXXXXXXX

Dose No.	Exposure year	Exposure rate	Radiation type	Organ Dose (cSv)
1	1955	Acute	Photon, E=30-200 keV	Lognormal(0.5,1.8)
2	1955	Acute	Photon, E>200 keV	Lognormal(0.7,1.8)
3	1956	Chronic	Neutron, E=100 keV-2 MeV	Lognormal(0.1,1.8)
4	1956	Acute	Photon, E>200 keV	Lognormal(0.4,2.5)
5	1957	Chronic	Alpha	Uniform(0.1,4)
6	1957	Acute	Photon, E>200 keV	Lognormal(1.3,1.8)
7	1958	Chronic	Alpha	Uniform(0.05,5.6)
8	1958	Acute	Photon, E>200 keV	Lognormal(0.2,1.8)
9	1959	Chronic	Neutron, E=100 keV-2 MeV	Lognormal(0.5,2.5)
10	1959	Acute	Photon, E>200 keV	Lognormal(0.1,1.8)
11	1960	Acute	Photon, E>200 keV	Lognormal(0.5,1.8)
12	1960	Chronic	Neutron, E=100 keV-2 MeV	Lognormal(0.1,2.5)
13	1961	Acute	Photon, E>200 keV	Lognormal(0.3,1.8)
14	1961	Chronic	Neutron, E=100 keV-2 MeV	Lognormal(0.2,2.5)
15	1962	Acute	Photon, E>200 keV	Lognormal(0.1,1.8)

RESULTS OF NIOSH-IREP

Assigned Share (Probability of Causation):

1 st percentile	0.0%
5 th percentile	0.0%
50 th percentile	0.70%
95 th percentile	3.84%
99th percentile	6.84%

Name of Analyst: _____

_____ Title: _____

_____ Signature: _____

_____ Date: _____

Name of Reviewer: _____

_____ Title: _____

_____ Signature: _____

_____ Date: _____

Appendix II: Glossary of ICD-9 codes and their cancer descriptions⁶

ICD-9 code	Cancer description
140	Malignant neoplasm of lip
141	Malignant neoplasm of tongue
142	Malignant neoplasm of major salivary glands
143	Malignant neoplasm of gum
144	Malignant neoplasm of floor of mouth
145	Malignant neoplasm of other and unspecified parts of mouth
146	Malignant neoplasm of oropharynx
147	Malignant neoplasm of nasopharynx
148	Malignant neoplasm of hypopharynx
149	Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx
150	Malignant neoplasm of esophagus
151	Malignant neoplasm of stomach
152	Malignant neoplasm of small intestine, including duodenum
153	Malignant neoplasm of colon
154	Malignant neoplasm of rectum, rectosigmoid junction, and anus
155	Malignant neoplasm of liver and intrahepatic bile ducts
156	Malignant neoplasm of gall bladder and extrahepatic bile ducts
157	Malignant neoplasm of pancreas
158	Malignant neoplasm of retroperitoneum and peritoneum
159	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum

⁶The International Classification of Diseases Clinical Modification (9th Revision) Volume I&II. [1991] Department of Health and Human Services Publication No. (PHS) 91-1260, U.S. Government Printing Office, Washington D.C.

ICD-9 code	Cancer description
160	Malignant neoplasm of nasal cavities, middle ear, an accessory sinuses
161	Malignant neoplasm of larynx
162	Malignant neoplasm of trachea, bronchus and lung
163	Malignant neoplasm of pleura
164	Malignant neoplasm of thymus, heart, and mediastinum
165	Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs
170	Malignant neoplasm of bone and articular cartilage
171	Malignant neoplasm of connective and other soft tissue
172	Malignant melanoma of skin
173	Other malignant neoplasm of skin
174	Malignant neoplasm of female breast
175	Malignant neoplasm of male breast
179	Malignant neoplasm of uterus, not otherwise specified
180	Malignant neoplasm of uterine cervix
181	Malignant neoplasm of placenta
182	Malignant neoplasm of uterine corpus (body of uterus)
183	Malignant neoplasm of ovary and other uterine adnexa
184	Malignant neoplasm of other and unspecified female genital organs
185	Malignant neoplasm of prostate
186	Malignant neoplasm of testis
187	Malignant neoplasm of penis and other male genital organs
188	Malignant neoplasm of urinary bladder
189	Malignant neoplasm of kidney and other and unspecified urinary organs
190	Malignant neoplasm of eye
191	Malignant neoplasm of brain
192	Malignant neoplasm of other and unspecified parts of nervous system

ICD-9 code	Cancer description
193	Malignant neoplasm of thyroid gland
194	Malignant neoplasm of other endocrine glands and related structures
195	Malignant neoplasm of other and ill-defined sites
196	Secondary and unspecified neoplasms of the lymph nodes
197	Secondary neoplasms of the respiratory and digestive organs
198	Secondary neoplasms of other tissue and organs
199	Malignant neoplasm without specification of site
200	Lymphosarcoma and reticulosarcoma
201	Hodgkin's disease
202	Other malignant neoplasms of lymphoid and histiocytic tissue
203	Multiple myeloma and other immunoproliferative diseases
204	Lymphoid leukemia
205	Myeloid leukemia
206	Monocytic leukemia
207	Other specified leukemia
208	Leukemia of unspecified cell type